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TELEFAX

For the Attention of Ms. NATALIA MORANCHO ALCAINE
Authorized Officer for the International Preliminary Examining Authority

Our ref.: 39123/ASI/rf

Re: International Patent Application
No. PCT/ EP 2004/ 005157
filed on May 13, 2004
in the name of: NAXOSPHARMA S.r.l.

Dear Madam,

INFORMAL COMMENTS

This is a reply to the Search Report and Written Opinion dated 30.09.2004, in connection with the above-identified application.

Hand-amended claims pages 16-18 containing a set of Claims 1-5 and hand-amended description pages 12 and 13 are herewith enclosed.

The amendments are made without prejudice. The Applicant does not intend to abandon any subject matter present in the original application.

The Examiner's objections are addressed below in the same order as presented in the Written Opinion.

It is noted that the novelty of the subject matter of claims 1-8 is acknowledged and that the subject matter of claims 1-8 is considered by the Examiner to lack an inventive step.

It is furthermore noted that the Examiner indicates that the subject matter of claims 1-5 differs from the disclosures of D1 in that the treatment is applied to animals and that the subject matter of claims 6-8 differs from the disclosures of D1 in that the aminopyrrolecarboxamide compounds are associated with cyclodextrin.
It is also noted that the Examiner indicates that D2 discloses that complexation of a compound with cyclodextrin avoids the compound to precipitate in physiologic conditions, and concludes that the subject mater of claims 6-8 lack, an inventive step.

Amended claim 1 corresponds to a combination of original claims 1 and 6 and is directed to the use of a compound of formula 1 in association or combination with cyclodextrin for preparing a pharmaceutical composition having activity against endoparasitosis in animals.

It should be noted that,

however, as stated in T 0852/91,

> *"To deny inventive step for novel chemical compounds because of their "structural similarity" to known chemical compounds amounts to an allegation that a skilled person would have reasonably expected the same or similar usefulness of both the known and the novel compounds as the means for solving the technical problem underlying the application in question. Such an expectation would be justified, if the skilled person knew, be it from common general knowledge or from some specific disclosure, that the existing structural difference of the chemical compounds concerned were so small that they would have no essential bearing on those properties, which are important for solving the said technical problem and could be disregarded"*

in the present case, no particular document was cited in support of the argument that the compound of formula I associated or combined with cyclodextrin of the claimed invention would act as an equivalent to the compounds disclosed in D1, in respect to the treatment of endoparasitosis

Moreover, the Applicant submits that there is nothing in the state of the art from which the skilled person would have deduced that the presence of the additional cyclodextrin with respect to the compounds of D1 would result in a complex still having activity of treating endoparasitosis.

Furthermore, in T 989/93 the Board stated that

> *"In the absence of the appropriate common general knowledge no conclusions are possible on the basis of the known properties of one group of chemical compounds (here benzene derivatives) regarding the properties of a different group of chemical compounds (here: naphthalene derivatives)."*

In the present case, a skilled person relaying of the disclosure of D1 about the properties of the compounds disclosed therein could not have reasonably expected that the compound of formula I associated or combined with cyclodextrin, as used in the present invention, exhibit the same properties. On the contrary, no reason was given why a skilled person would have applied information regarding the the compounds of D1 to the compounds of formula I associated or combined with cyclodextrin of the claimed invention, in the treatment of endoparasitosis.

It should be noted that the association or combination of drugs with cyclodextrin do not necessarily lead to pharmaceutically active complexes. On the contrary, in some cases the complexes do not have the therapeutic effect of the drug or have therapeutic effects reduced with respect to those of the drug. Thus, no prediction can be made regarding the therapeutic activity of such complexes.

In fact, even if it is known that certain drugs can be complexed with cyclodextrin, no basis can be found for a generalisation regarding the concept of complexion of drugs with cyclodextrin and regarding the activity or behaviour of the obtained complexes. Particularly, D2 does not show or suggest the fact that the association or combination of a compound of formula I with cyclodextrin has improved effects with respect to the compound of formula I alone, such as precipitation in physiological conditions.

Thus, it cannot be said that the skilled person, in expectation of the advantages actually achieved, WOULD have arrived at the claimed invention by modifying the teaching of D1 by adding cyclodextrin to the compounds disclosed therein, because of promptings in the prior art. There is no recognisable pointer in the prior art to add cyclodextrin to the compounds of D1 so as to arrive to the claimed subject matter.

In addition, obvious transcription errors were corrected in Claim 1 by replacing among the meanings of X "oxygen" with "hydrogen" and by including among the meanings of R1 the meaning already specified in claim 2 that is "-CH2N(CH3)2". With these corrections, the discrepancies pointed out by the Examiner between the formulation of claim 1 and of claim 2 were overcome.
It is accordingly submitted that the claims are in acceptable condition.

In addition, the changes have been made in the description, on page 11-13, to correct an obvious typing error, i.e. to change "-COONH2" to read change "-CONH2". With these corrections, the discrepancies pointed out by the Examiner between the exemplified compounds and the definition of the compounds of formula I were overcome.

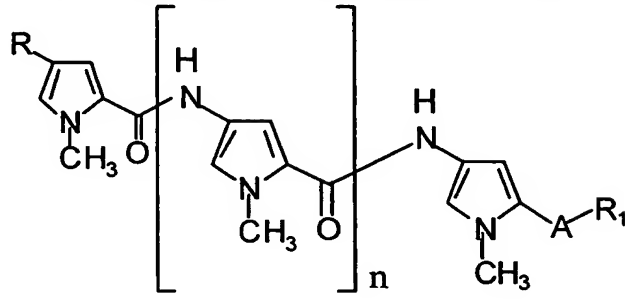
Respectfully submitted,

Guido MODIANO
Professional Representative for the Applicant

Enclosures: Hand-Amended description pages 12-13;
Hand-Amended Claims pages 16-18.

CLAIMS

1. Use of a compound having the following formula (I):



I

wherein:

n is 0 or an integer comprised between 1 and 5;

R is a group R_2-X -C(=Z)-NH-, in which X represents a simple chemical bond, an aromatic or heteroaromatic radical, Z represents an oxygen atom or the NH group; and:

if X is a simple chemical bond, R_2 is an ~~oxygen~~ hydrogen atom, an alkyl, dialkylaminoalkyl, alkenyl, cycloalkyl, arylalkyl, arylalkenyl, haloalkyl, or an aromatic or heteroaromatic radical;

if X is an aromatic or heteroaromatic radical, R_2 is nitro, amino or formylamino;

or:

R is a group R_3-C(=Z)-, in which Z represents an oxygen atom or the NH group, and R_3 represents a hydrogen atom, the -OR_4 or -NR_5R_6 group, and where:

R_4 is chosen from the group consisting of a hydrogen atom, an alkyl, cycloalkyl, arylalkyl, or an aromatic radical;

R_5 and R_6, either the same or different, are chosen from the group consisting of a hydrogen atom, an alkyl, cycloalkyl, arylalkyl, aromatic or

heterocyclic radical, optionally substituted with a formylamino or a carbamoyl group; or

R_5 and R_6, joined together form an alkylene group, or the group $-(CH_2)_2-O-(CH_2)_2-$ or the group $-(CH_2)_2-NH-(CH_2)_2-$;

A represents a simple chemical bond or the group -CO-NH-Y-, wherein Y is an alkylene or aromatic radical;

R_1 is chosen from the group consisting of $-COOR_4$, $-B-NR_5R_6$, $-C(=NH)-NH_2$, a heterocyclic radical containing nitrogen, wherein:

R_4, R_5 and R_6 are as defined above, B represents a simple chemical bond or the -C=O group, and:

when R_1 is $-B-NR_5R_6$, and B is a simple chemical bond, or when R_1 is a heterocyclic radical, A is not a chemical bond;

or a pharmaceutical acceptable salt thereof ~~in the manufacture of a pharmaceutical composition having activity against endoparasitosis in animals.~~

2. Use according to Claim 1, where the compound of formula (I) is chosen between distamycin and a compound of formula (I) wherein:

n is as previously defined;

R is the $-CONH_2$ group, A is the $-CONHCH_2CH_2-$ group, R_1 is the $-C(=NH)-NH_2$ group or the $-CH_2N(CH_3)_2$ group;

R is the -NH-CH(=NH) group, A is the $-CONHCH_2CH_2-$ group, R_1 is the $-C(=NH)-NH_2$ group or the $-CH_2N(CH_3)_2$ group or the $-CONH_2$ group;

and the pharmaceutically acceptable salts thereof.

~~3. Use according to Claim 1, where the pharmaceutical composition is for oral use.~~

~~4. Use according to Claim 1, where the pharmaceutical composition is for the prophylaxis and/or treatment of endoparasitosis in animals.~~

5. Use according to Claim 4, where the endoparasitosis is chosen from Trichomoniasis, Giardiasis, Istomoniasis, Amoebiasis, Coccidiosis, and Balantidiosis.

~~6. Use of a compound of formula (I), or a pharmaceutically acceptable salt thereof,~~ [in association or combination with a cyclodextrin in the manufacture of a veterinary pharmaceutical composition having activity against endoparasitosis in animals.]

3 ~~7.~~ Use according to Claim ~~6~~ 1, where the pharmaceutical composition is for oral use.

4 ~~8.~~ Use according to Claim ~~6~~ 1, where the pharmaceutical composition is for the prophylaxis and/or treatment of endoparasitosis in animals.

variable concentrations of hydrochloride of the compound of formula (I, R = -CONH2, ~~-COONH2,~~ A = -$CONHCH_2CH_2$-, R_1 = -C(=NH)-NH_2) dissolved in dimethylsulphoxide (DMSO) or DMSO (5% medium) in controls. The test compound was removed 30 minutes later by repeated washings. The percentage of infected cells was determined 24 hours after beginning of experiment by microscopic examination after Giemsa staining, analysing 10 microscopic fields for each experimental point at 400x. The values obtained for each point represent the mean of three independent replicates. The percentage of infected cells in untreated controls (i. e., treated with DMSO only) was 7.1% for Experiment 1, and 6.35 for experiment 2. Results set forth in Figure 1 show a remarkable cytotoxic activity of the test compound against the object parasite.

Example 2

In vivo activity. The in vivo oral antiparasitic activity of the compound of formula (I, R = -CONH2, ~~-COONH2,~~ A = -$CONHCH_2CH_2$-, R_1 = -C(=NH)-NH_2) was assessed by evaluating the ability of test compound to modify the course of experimentally induced infection in immuno-suppressed BALB/C mice. After several weeks of immunosuppressive treatment with dexamethasone, 30 mice were orally infected with *C. parvum* oocysts on the same day. Two weeks after infection, mice shedding oocysts, identified by detecting oocysts in the stools using both Zeil Niessel staining and immunofluorescence, were pooled in three groups of 5 animals each. Two groups were treated with hydrochloride of the test compound dissolved in drinking water at a concentration of 5 μg/mL (mice are expected to drink about 2 -5 mL of water per day), whereas the third group (control group) did not receive any treatment. To evaluate the efficacy of the treatment, the shedding of oocysts was monitored for 4 weeks. Animals receiving treatment showed a significant reduction in oocyst shedding after 1 week, and

oocysts could not be detected after 2 weeks of treatment with the test compound, and remained parasite free until the end of the experiment (4 weeks).

Example 3

10 male Sprague-Dawley rats weighing 320 - 390 g were used with the scope to determine plasma levels of the compound of formula (I, R = ~~-COONH2,~~ -CONH2, A = -$CONHCH_2CH_2$-, R_1 = -C(=NH)-NH_2) after intravenous and oral administration, respectively. Rats were anesthetized and the right jugular vein was cannulated and the cannula was left exposed on the neck to allow for drug administration and blood collection. Rats were administered 24 - 48 hours after recovery from surgical anesthesia.

Intravenous drug administration (10 mg/kg). 10 mg of hydrochloride of the test compound were dissolved in a vehicle constituted of DMSO and saline buffer (1 : 20 v/v) at a concentration of 1.5 mg/mL. The administered volume was 2 mL/kg as bolus.

Oral administration (20 mg/kg). 20 mg of hydrochloride of the test compound were dissolved in a vehicle constituted of DMSO and saline buffer (1 : 250 v/v) at a concentration of 5 mg/mL. The administered volume was 5 mL/kg.

Sample collection. Blood samples (400-500 µl) were withdrawn from jugular vein at intervals of 0, 5, 15, 30, 60, 90, 120, 180, 240, 360, 480, 680 and 1440 minutes after intravenous and oral administration, respectively, of test drug. The amount of collected blood was replaced by an equal volume of saline.

Plasma levels. The determination of test compound blood levels was performed by using a validated HPLC method. The limit of quantitation of the assay was 0.1 µg/0.5 mL.

After a single intravenous administration of 10 mg/kg of the drug, the mean drug concentration in blood declined according to a biexponential profile.